Appendix C

Krieg '646 Patent Claims Corresponding to Proposed Count 1

Composition claims

Claims 6-11 and 13.[5] Claim 6 (directed to a plasmid) is generic to the subgenus which is the second alternative of proposed count 1. Claims 7-11 are dependent claims which do not define separate patentable inventions. Claim 7 is identical to the second alternative of proposed count 1; it recites a Markush group directed to a subgenus of sequence combinations of X_1X_2 and X_3X_4. One species, namely AACGTT, is anticipated by the first alternative of proposed count 1. Claim 8 recites that the composition further comprises a B-cell targeting molecule. Inclusion of a targeting moiety does not render the claimed plasmid patentably distinct from a plasmid without the targeting moiety. Claim 9 recites a Markush group directed to species of the B-cell targeting molecule of claim 8, at least one of which is obvious in view of a B cell targeting moiety (*e.g.*, a B-cell specific binding agent). Claim 10 recites that the antigen is "encoded in a DNA vaccine". The patentably indistinct nature of "antigen" and antigen "encoded in a DNA vaccine" was discussed above. Claims 11 and 13 recite Markush groups directed to species of antigen, and at least one member of the Markush group is an obvious species of antigen (*e.g.*, "protein", "derived from an infectious organism. . .infectious bacteria").

Claims 14-17. Claim 14 is directed to a composition containing a CG-containing immunostimulatory nucleic acid sequence of 8 to 100 nucleotides in length[6] with antigen. Claim 14 (to an oligomer) is not patentably distinct in view of a count directed to a plasmid; an oligomer is obvious in view of a plasmid. As is well known in the art, a plasmid is a circular polynucleotide. A linear, oligomeric form of a polynucleotide containing the same sequence as the plasmid is a predictable form of a polynucleotide in view of a plasmid. Both carry the same

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[5] Applicants note that claim 12 of this series of claims is deliberately omitted. This claim does not correspond to proposed count 1, as this claim is directed to patentably distinct subject matter and is to be the subject of a separate count (count 2) within this interference.

[6] As presented in the formula "X_1CGX_2", wherein X_1 and X_2 are nucleotides.

functional sequence. The Krieg '646 patent specification refers both to oligomers and "DNA vaccines", which are plasmids ("When the vaccine is a DNA vaccine. . ." Col. 33, line 38). Further, the Krieg '646 patent specification states that oligomers of 8 to 40 base pairs are preferably used for economic reasons, and that, alternatively, the "CpG dinucleotides can be produced on a large scale in plasmids, which after being administered to a subject are degraded into oligonucleotides". Col. 11, lines 39-44. Claims 15-17 are dependent claims which do not define separate patentable inventions. Claim 15 adds the limitation that the oligomer has a phosphate backbone modification (which is a phosphorothioate or phosphorodithioate modification), which is not patentably distinct in view of proposed count 1, as this is an obvious DNA modification. Phosphate backbone modifications, such as a phosphorothioate or phosphorodithioate modifications, are well known in the art as stabilizing modifications which provide nuclease resistance to such modified polynucleotides. *See, for example*, Crooke (1992) *Annu. Rev. Pharmacol. Toxicol.* 32:329-376; Milligan et al. (1993) *J. Med. Chem.* 36:1923-1937. The Krieg '646 patent specification accordingly describes the use of such phosphate backbone modifications in immunostimulatory oligonucleotides for stability and resistance to *in vivo* degradation by nucleases. *See, e.g.,* col. 6, lines 47-49; col. 12, lines 45-63. Claim 16 recites that the antigen is encoded in a DNA vaccine. "Antigen" and antigen "encoded in a DNA vaccine" (plasmid) are patentably indistinct, as discussed above. Claim 17 recites a Markush group directed to species of antigen, and at least one member of the Markush group is an obvious species of antigen (e.g., protein).

Claims 18-21; 30. Claim 18 is directed to a composition containing a CG-containing immunostimulatory nucleic acid sequence of at least 8 nucleotides in length[7] with antigen. This claim is not patentably distinct from proposed count 1 as it is anticipated by the proposed count (species anticipating the genus). Claims 19-21 and 30 are dependent claims which do not define separate patentable inventions. Claim 19 adds the limitation that the immunostimulatory nucleic

[7] As presented in the formula "X_1CGX_2", wherein X_1 and X_2 are nucleotides.

acid has a phosphate backbone modification (which is a phosphorothioate or phosphorodithioate modification), which is not patentably distinct in view of proposed count 1, as this is an obvious DNA modification, as discussed above. Claim 20 recites that the antigen is encoded in a DNA vaccine. "Antigen" and antigen "encoded in a DNA vaccine" (plasmid) are patentably indistinct, as discussed above. Claim 21 recites a Markush group directed to species of antigen, and at least one member of the Markush group is an obvious species of antigen (*e.g.*, protein). Claim 30 is directed to an oligomer which is 8 to 100 nucleotides in length. As discussed above, an oligomer is obvious in view of the plasmid composition of proposed count 1.

Claims 22-25. Claim 22 is directed to a composition containing a CG-containing immunostimulatory nucleic acid sequence of 8 to 40 nucleotides in length[8] with antigen. Claim 22 (to an oligomer) is not patentably distinct in view of a count directed to a plasmid; an oligomer is obvious in view of a plasmid, as discussed above. Claims 23-25 are dependent claims which do not define separate patentable inventions. Claim 23 adds the limitation that the immunostimulatory nucleic acid has a phosphate backbone modification (which is a phosphorothioate or phosphorodithioate modification), which is not patentably distinct in view of proposed count 1, as this is an obvious DNA modification (discussed above). Claim 24 recites that the antigen is encoded in a DNA vaccine, which was discussed above. Claim 25 recites a Markush group directed to species of antigen, and at least one member of the Markush group is an obvious species of antigen (*e.g.*, protein).

Claims 31-37; 39.[9] Claim 31 is directed to a composition containing a CG-containing immunostimulatory nucleic acid sequence of at least 8 nucleotides in length[10] with antigen. This is anticipated by either alternative of proposed count 1. The claim further recites that "at least

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[8] As presented in the formula "X_1CGX_2", wherein X_1 and X_2 are nucleotides.

[9] Applicants note that claim 38 of this series of claims is deliberately omitted. This claim does not correspond to proposed count 1, as this claim is directed to patentably distinct subject matter and is to be the subject of a separate count (count 2) within this interference.

[10] As presented in the formula "$X_1X_2CGX_3X_4$", wherein X_1 -X_4 are nucleotides.

one nucleotide has a phosphate backbone modification." This is obvious in view of proposed count 1, as this is an obvious DNA modification, as discussed above, and thus this claim corresponds to the count. Claims 32-37 and 39 are dependent claims which do not define separate patentable inventions. Claim 32 is directed to an oligomer of 8 to 100 nucleotides in length. As discussed above, an oligomer is obvious in view of proposed count 1, which is directed to a plasmid. Claims 33 and 34 provide sequence permutations for X_1X_2 and X_3X_4, respectively. The only sequence exclusions for X_1X_2 in claim 33 based on the recited sequence permutations are X_1C (i.e., GC, AC, CC, and TC); all other sequence combinations for X_3X_4 are encompassed by this claim. Both alternatives of proposed count 1 recite a species within the claimed sequences, namely AACGTT, and thus anticipate this Markush group. The only sequence exclusions for X_3X_4 in claim 34 based on the recited sequence permutations are GX_4 (i.e., GT, GG, GC, and GA); all other sequence combinations for X_1X_2 are encompassed by this claim. Both alternatives of proposed count 1 recite a species within the claimed sequences, namely AACGTT, and thus anticipate this Markush group. Claim 35 recites that the immunostimulatory nucleic acid is associated with a cationic lipid, which is obvious in view of proposed count 1. As is well known in the art, nucleic acids may be associated with cationic lipids for delivery purposes. Claim 36 is directed to recited sequence combinations of X_1X_2 and X_3X_4, including AACGTT, which is recited in both alternatives of proposed count 1. Claims 37 and 39 recite Markush groups directed to species of antigen, and at least one member of each Markush group is an obvious species of antigen (e.g., protein; derived from an infectious bacteria).

Method claims

Claims 1 and 2. Claim 1 is directed to an *ex vivo* method for ameliorating an immune system deficiency by contacting lymphocytes with an immunostimulatory nucleic acid (which can be synthetic or have a phosphate backbone modification) of at least 8 nucleotides containing CG (as "X_1CGX_2", unmethylated C, X_1 and X_2 as any nucleotide) and an antigen to produce

activated lymphocytes, which are readministered. This is an obvious use of the immunostimulatory nucleic acids in view of the immunostimulatory composition of proposed count 1. The composition of the proposed count has immunostimulatory properties, and it was known in the art that *ex vivo* methods could be used to remove cells of interest from an individual, treat them *ex vivo*, and re-introduce the cells. Thus, using the composition of the proposed count to stimulate lymphocytes ex vivo is obvious in view of the composition. Claim 2 recites a Markush group directed to species of diseases, and at least one member of the Markush group is an obvious species of disease.

Claim 4. Claim 4 is directed to a method of vaccination comprising "administering to the subject a vaccine antigen or an antigen encoded in a DNA vaccine" and a CG-containing immunostimulatory nucleic acid (as "$X_1X_2CGX_3X_4$", unmethylated C, X_1 - X_4 any nucleotide). This is an obvious use of immunostimulatory nucleic acids in view of proposed count 1 and thus corresponds to the count. The Krieg '646 patent specification describes that the immunostimulatory nucleic acids provide adjuvant activity and elicit an antigen-specific immune response. *See, for example*, col. 33, lines 49-55. Thus, use of the immunostimulatory nucleic acids with an antigen in a vaccine is obvious in view of the immunostimulatory composition of proposed count 1.

Claims 26-29. Claim 26 is directed to a method of inducing an antigen-specific immune response by administering a vaccine containing an antigen and any of the immunostimulatory nucleic acids of claims 6, 14, 18 or 22, which have been discussed above. Using those compositions to generate an antigen-specific immune response in view of the composition of proposed count 1 is obvious and not patentably distinct because these compositions have immunostimulatory properties and the ability to elicit an antigen-specific immune response. *See, for example*, Krieg '646 patent at col. 33, lines 49-55. Claim 27 recites a Markush group directed to species of antigens to be used in the claimed method. At least one member of the Markush group is an obvious species of antigen (*i.e.*, protein). Claim 28 is directed to removing leukocytes from a subject and re-administering them after contact with the antigen (*i.e.*, *ex vivo*

methods). As discussed above, this is an obvious use of the claimed method. Claim 29 is directed to *ex vivo* administration, which is an obvious use of the claimed method.

Applicants submit that the above claims do not define separate patentable inventions within the meaning of 37 C.F.R. § 1.601(n).